

Claims 32-39 stand rejected as being obvious under 35 USC §103(a) over the lost interference count, and further in view of an excerpt of (1) a textbook authored by Benjamin Lewin, titled Genes IV, Oxford University press, 1990, pp. 70-73 (hereinafter referred to as the Lewin textbook); (2) an article by Culver et al., titled "Tobacco Mosaic ...," Virology, 173, 1989, pp. 755-758 (hereinafter referred to as the Culver article); (3) US Pat. No. 5,328,688 to Roizman (hereinafter referred to as the '688 patent); (4) PCT application No. WO 91/02795 (hereinafter referred to as the '795 application); and, (5) US Pat. No. 5,279,965 to Keeler, Jr. (hereinafter referred to as the '965 patent).

Applicants respectfully request reconsideration.

It is the Examiner's contention that, "even in the absence of specific direction, one of ordinary skill in the art would have been motivated to use one or more well-known means to avoid reversion of a useful mutation." See Advisory Action mailed July 24, 2001, p. 2. However, it is Applicants' contention that such a conclusion is based upon impermissible hindsight. The prior art relied upon by the Examiner does not establish a prima facie case of obviousness.

It is well accepted law that to establish a prima facie case of obviousness the analysis of several factors is required, including (1) determining the scope and content of the prior art; (2) determining the differences between the prior art and the claims at issue; (3) determining the level of ordinary skill in the art; and, if necessary to refute a showing of obviousness, (4) a showing of objective indicia of non-obviousness. Here, the Examiner has failed to apply the test and the rejection cannot stand.

A. Scope and Content of the Prior Art

1. What the Cited References Disclose

To begin, the Examiner contends that the Lewin textbook would make one of ordinary skill in the art aware that single base mutations are "leaky" and revertible. The Examiner then makes a leap that one of ordinary skill in the art would have been aware that a virus with multiple nucleotide changes would be less likely to revert to the undesired wild-type VP5 coding sequence. However, the Lewin textbook does not disclose or teach a mutation that comprises the substitution of at least two nucleotides of a start codon to substantially prevent reversion. Rather, the Lewin textbook teaches the terms neutral substitutions (silent mutations), forward mutations (original mutation), back mutations (mutations that reverse forward mutations), true reversions (the act of back mutations), and second-site reversions (the act of a subsequent mutation that has the effect of compensating for the first mutation). The teachings and disclosure of the Lewin textbook is directed towards mutations and reversions of those mutations. There is no disclosure that making two mutations in a start codon will affect reversion of a gene.

The Examiner contends that the Culver article teaches and discloses that alteration of more than one nucleotide to remove a start codon has been known for years in the virology art. However, the teachings of the Culver article is not that a mutation and/or alteration of the more than one nucleotide to remove a start codon in any manner affects reversion. The Culver article addresses the issue of whether the coat protein or the altered viral RNA was responsible for hypersensitive regions. There is no teaching and/or disclosure of a mutation that comprises the substitution of at least two nucleotides of a start codon to substantially prevent reversion. Instead, the Culver article teaches removal of a coat protein.

The Examiner contends that the '688 patent teaches the use of multi-frame stop codons to prevent expression of an unwanted gene. The Examiner directs Applicants to Column 16, lines 16-20 of the '688 patent for support for the contention. However, Column 16 lines 16-20 of the '688 patent discloses nothing more than a virus constructed to contain translational stop codons in all three reading frames in the beginning of the ICP34.5 coding sequence. The patent specifically states that this was done to eliminate the possibility that the phenotype of R3616 reflects deletion in cryptic open reading frames. Accordingly, there is no teaching and/or disclosure of a mutation that comprises the substitution of at least two nucleotides of a start codon to substantially prevent reversion.

The Examiner contends that the '795 application teaches the use of multi-frame stop codons to prevent expression of an unwanted gene. The Examiner directs Applicants to the passage spanning pages 6-7 for support for the contention. However, this passage teaches nothing more than in the investigation of the influence of the defunctionalization of the PRV protein kinase and 28K gene and that an oligonucleotide was inserted in each that had stop codons in each of the possible three reading frames. No further teaching is present in the patent. Accordingly, there is no teaching and/or disclosure of a mutation that comprises the substitution of at least two nucleotides of a start codon to substantially prevent reversion.

The Examiner contends that the '965 patent also teaches the use of multi-frame stop codons to prevent expression of an unwanted gene. The Examiner specifically directs Applicants to Column 3, line 52 to Column 4, line 8. This excerpt of the '965 patent only discloses inserting translational stop codons in each of the three possible

reading frames, in both directions. There is no teaching and/or disclosure of a mutation that comprises the substitution of at least two nucleotides of a start codon to substantially prevent reversion.

2. The Examiner's summation of the rejection

The Examiner then contends that the lost count in the interference in this application requires a virus which is not able to produce VP5 as a result of a mutation in the VP5 gene, it would have been obvious to choose forms of mutation which were known to prevent production of a protein. However, the Examiner has not, in any instance, shown any suggestion and/or motivation to modify any of the references to arrive at Applicants' invention. The Examiner has only picked pieces of the prior art from five different references and stated that the ordinary skill in the art was motivation to modify the lost interference count. However, it is Applicants' contention that the prior art does not teach and/or suggest such a modification.

B. The Differences Between the Prior Art and the Claims at Issue

Claims 32-39 vary dramatically from the prior art. First, it is important that the Examiner agrees with Applicants that "neither the count nor the Mundt reference specifies a non-reverting mutation which comprises the substitution of at least two nucleotides of the start codon." See Final Rejection of March 13, 2001, p. 2. However, it is the next statement by the Examiner with which Applicants strongly disagree. The Examiner then contends that because "reversion of single point mutations was a well-known phenomenon, ... one of ordinary skill **would not require** particular direction or specific teachings" to arrive at Applicants' invention. See Final Rejection of March 13,

2001, p. 2 (Emphasis Added). As the Examiner has stated, this rejection contains no specific teachings in the prior art to arrive at Applicants' invention. The Examiner is relying upon the ordinary skill in the art to supply that which is not present in the prior art.

There can be no dispute that the Lewin textbook never discloses and/or teaches, in any manner, how to prevent reversion. In fact, the Lewin textbook talks about reversion through the use of "back mutations" and "second-site mutations." This is not a disclosure and/or teaching of Applicants' invention. Moreover, it cannot be said that teaching reversion of mutation in some manner suggests and/or motivates one of ordinary skill in the art to prevent reversion. Reversion and preventing reversion are two different fields and, in fact, teach away from one another. Accordingly, there is a great difference between the Lewin textbook and Applicants' invention.

Further, there can be no dispute that the Culver article never discloses and/or teaches that a mutation and/or alteration of the more than one nucleotide to remove a start codon affects reversion. As stated, the Culver article disclosed mutations for determining which part of a gene was responsible for hypersensitive regions. There is no teaching and/or disclosure of preventing reversion by a mutation that comprises the substitution of at least two nucleotides of a start codon. Accordingly, there is a great difference between the Lewin textbook and Applicants' invention.

Likewise the '688 patent, the '795 application, and the '965 patent do not teach any aspect of reversion. These patents solely contain mutation in the reading frames. There is no teaching and/or disclosure of preventing reversion by a mutation that comprises the substitution of at least two nucleotides of a start codon. The '688 patent,

the '795 application, and the '965 patent offer no motivation and/or suggestion to arrive at Applicants' invention. Accordingly, there is a great difference between the Lewin textbook and Applicants' invention.

C. The Level of ordinary skill in the art

The level of ordinary skill in the art can be ascertained from the 132 Declaration of Egbert Mundt signed on November 24, 2000 and submitted with Applicants' Amendment of December 11, 2000. (also, attached as Exhibit A). From this table, coupled with the teachings from the lost interference count, one of ordinary skill in the art at the time of Applicants' invention would have considered one mutation in the VP5 gene as stable, requiring no further change. This is evidenced by the Examiners cited prior art. In no instance in the cited prior art were multiple mutations performed to substantially prevent reversion, to increase stability of the mutated gene. This fact is even more apparent from the absence in the art of any serial passage data that attempted to determine stability of the mutation. Accordingly, one of ordinary skill in the art at the time of Applicants' invention would have assumed that one mutation (a single mutation) in the VP5 gene would have been stable. There is a complete lack of teaching and/or disclosure in the prior art to motivate and/or suggest otherwise.

D. Objective Indicia of Non-obviousness

Egbert Mundt's Section 132 Declaration mentioned above and attached as Exhibit A provides unexpected results. It can be clearly seen that, in every case, by the ninth serial passage of IBDV/VP5-, reversion was experienced. Applicants' invention

demonstrates that serial passage of IBDV/VP5-2 up to 18 times experienced no reversion. The Examiner contends that this is the expected result, but has provided no reference that suggests these results. Accordingly, this is valid data of unexpected results and strong indicia of non-obviousness.

E. The rejection is improper

The Examiner has established obviousness based upon Applicants' disclosure, using impermissible hindsight without a correct test for obviousness. It is fundamental that a proper determination of the scope of the prior art incorporates an examination of the field of the inventor's endeavor. *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 58 F.2d 613, 620 (Fed. Cir. 1985), Of particular concern is the particular problem with which the inventor was involved. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1535 (Fed. Cir. 1983) (*quoting In re Wood*, 599 F.2d 1032, 1036 (CCPA 1979)). Here, the prior art lost interference count contained a single mutation in the VP5 gene. The prior art, as reflected by the art cited by the Examiner, considered this mutation stable. It was not until Applicants' invention that the lack of stability of a single mutation in the VP5 gene was identified and solved. There is no other teaching and/or disclosure in the prior art.

The Examiner has used hindsight reasoning to define the problem in terms of its solution. *See, e.g., In re Antle*, 444 F.2d 1168, 1171-72 (CCPA 1971) (warning against selection of prior art with hindsight). The prior art chosen by the Examiner does not address the problem solved by Applicants, but rather attempts to supply unrelated individual elements.

It has long been the law that identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. *See id.* Rather, to establish obviousness based on a combination of elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant. *See In re Dance*, 160 F.3d 1339, 1343 (Fed. Cir. 1998); *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984). Here, the Examiner has failed to demonstrate any motivation and/or suggestion. Instead, the Examiner relies upon the level of ordinary skill in the art. However, the facts of the present application do not support the Examiner's rejection, as the level of ordinary skill in the art indicates otherwise.

Rarely, if ever, will the skill in the art component operate to supply missing knowledge or prior art to reach an obviousness judgment. *See W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed.Cir.1983) ("To imbue one of ordinary skill in the art with knowledge of the invention in [issue], when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher."). It has long been understood that skill in the art does not act as a bridge over gaps in substantive presentation of an obviousness case, but instead supplies the primary guarantee of objectivity in the process. *See Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991). Here, the Examiner wholly relies on the level of ordinary skill in the art to supply elements that are wholly missing in the prior art, namely any motivation and/or suggestion.

The Federal Circuit has made it abundantly clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. *See, e.g., C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1352 (Fed. Cir. 1998) (describing "teaching or suggestion or motivation [to combine]" as an "essential evidentiary component of an obviousness holding"); *In re Rouffet*, 149 F.3d 1350, 1359 (Fed. Cir. 1998) ("the Board must identify specifically . . . the reasons one of ordinary skill in the art would have been motivated to select the references and combine them"); *In re Fritch*, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (examiner can satisfy burden of obviousness in light of combination "only by showing some objective teaching [leading to the combination]"); *In re Fine*, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) (evidence of teaching or suggestion "essential" to avoid hindsight); *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 297, 227 USPQ 657, 667 (Fed. Cir. 1985) (district court's conclusion of obviousness was error when it "did not elucidate any factual teachings, suggestions or incentives from this prior art that showed the propriety of combination"). *See also Graham*, 383 U.S. at 18 ("strict observance" of factual predicates to obviousness conclusion required). The Examiner's combination of the prior art without evidence of such a suggestion, teaching, or motivation simply takes Applicants' disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. *See, e.g., Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138, 227 USPQ 543, 547 (Fed. Cir. 1985) ("The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time."). Here, there

has been no motivation and/or suggestion pointed out by the Examiner to arrive at Applicants' invention. Therefore, the use of ordinary skill in the art to supply the missing elements is inappropriate and the rejection wrong.

Stated another way, a determination of obviousness can not be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention. There must be a teaching or suggestion within the prior art. *See Heidelberg Druckmaschinen AG v. Hantscho Commercial Prods., Inc.*, 21 F.3d 1068, 1072 (Fed. Cir. 1994) ("When the patented invention is made by combining known components to achieve a new system, the prior art must provide a suggestion or motivation to make such a combination."); *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 935 (Fed. Cir. 1990) (the prior art must suggest to one of ordinary skill in the art the desirability of the claimed composition); *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985). Therefore, the rejection is wrong.

There can be no dispute that obviousness is a question of law based on findings of underlying facts relating to the prior art, the skill of the artisan, and objective considerations. *See Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). To establish a prima facie case of obviousness based on a combination of the content of various references, there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant. *In re Raynes*, 7 F.3d 1037, 1039 (Fed. Cir. 1993); *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992). The Federal Circuit has made it clear that it is the prior art itself, and not the Applicants' invention, that must establish the obviousness of the combination. *Interconnect Planning Corp. v.*

Feil, 774 F.2d 1132, 1143 (9th Cir. 1985). Here, the Examiner admitted that the prior art did not contain the elements of Applicants' invention. Therefore, a prima facie case of obviousness has not been established.

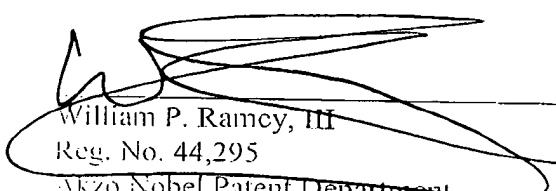
II. Conclusion

Applicants respectfully request reconsideration of the rejections in light of this response. The application is believed in a condition for allowance and Applicants respectfully request such action. Please call the below undersigned attorney for any assistance in securing allowance of this application. Please charge deposit account number 02-2334 for any required fees.

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4/4/02

Sincerely,



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